Annals of Oncology 23: 1838–1845, 2012
doi:10.1093/annonc/mdr540
Published online 18 November 2011

Fasting glucose and treatment outcome in breast and colorectal cancer patients treated with targeted agents: results from a historic cohort

M. Barba[1,2*], F. Sperati[3], S. Stranges[4], C. Carlomagno[5], G. Nasti[6], V. Iaffaioli[6], G. Caolo[3], M. Mottolese[7], G. Botti[8], I. Terrenato[3], P. Vici[9], D. Serpico[5], A. Giordano[1,2], G. D'Aiuto[10], A. Crispo[11], M. Montella[11], G. Capurso[12], G. Delle Fave[12], B. Fuhrman[3], C. Botti[13] & S. De Placido[5]

[1]Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, Temple University, Philadelphia, USA; [2]Human Health Foundation, Spoleto-Terni; [3]Department of Epidemiology, Regina Elena National Cancer Institute, Rome, Italy; [4]Health Sciences Research Institute, University of Warwick Medical School, Coventry, UK; [5]Department of Medical Oncology and Endocrinology, Federico II Medical School of Naples, Naples; [6]Department of Colorectal Medical Oncology, G. Pascale National Cancer Institute, Naples; [7]Department of Pathology, Regina Elena National Cancer Institute, Rome; [8]Departmental Unit of Pathology and Cytopathology, G. Pascale National Cancer Institute, Naples; [9]Division of Medical Oncology B, Regina Elena National Cancer Institute, Rome; Departments of; [10]Senology; [11]Epidemiology, G. Pascale National Cancer Institute, Naples; [12]Digestive and Liver Disease Unit, II Medical School, University La Sapienza, Rome; [13]Department of Surgery, Regina Elena National Cancer Institute, Rome, Italy

Received 1 April 2011; revised 3 October 2011; accepted 5 October 2011

Background: We investigated pretreatment fasting glucose as a predictor of patients' important outcomes in breast and colorectal cancers undergoing targeted therapies.
Patients and methods: In a historic cohort of 202 breast and 218 colorectal cancers treated with targeted agents from 1998 to 2009, we used the Kaplan–Meier method and the log-rank test to estimate survival through tertiles of fasting glucose and the Cox proportional hazards model for multivariate analysis stratified by primary site of cancer and including gender, age and body mass index.
Results: The median follow-up was 20 months (1–128). At 60 months, 65% of patients in the lowest tertile of fasting glucose did not experiment disease progression compared with 34% in the highest tertile ($P = 0.001$). Seventy-six percent of females in the lowest tertile showed no progression compared with 49% in the top tertiles ($P = 0.015$). In multivariate analysis, fasting glucose was a significant predictor of time to disease progression only in breast cancer patients in the first tertile compared with the third ($P = 0.017$).
Conclusions: We found evidence of a predictive role of pretreatment fasting glucose in the development of resistance in breast cancer patients treated with targeted agents. Prospective studies are warranted to confirm our findings.
Key words: breast cancer, colorectal cancer, fasting glucose, targeted agents

introduction

The increasing understanding of molecular pathways regulating cell cycle, apoptosis, angiogenesis and invasion has provided new targets in cancer therapy [1, 2]. The biologic agents trastuzumab [a humanized blocking antibody against the human epidermal growth factor receptor 2 (HER2)/neu receptor], bevacizumab [an inhibitor against vascular endothelial growth factor (VEGF)] and cetuximab [an mAb to the epidermal growth factor receptor (EGFR)] received United States Food and Drug Administration (US FDA) approval for breast and colorectal cancer treatment [http://www.cancer.gov/cancertopics/treatment/druginformation, (3 November 2011, date last accessed)].

The identification of biomarkers that are likely to predict which patients will achieve the best response to these agents represents a major challenge for contemporary oncologists.

The current tendency to characterize reliable predictors of response to target therapy runs in parallel with the recently emerging theme of the cross talk between different families of receptors in response to ligand activation. In these respects, extensive preclinical work supports the signaling interaction between factors related to glucose metabolism (fasting glucose, insulin-like growth factors), VEGFs and members of the erbB tyrosine kinase family, such as the EGFR and HER2 [3–9].

Several epidemiologic studies support the role of glucose metabolism in breast and colorectal carcinogenesis. Two distinct meta-analyses of case–control and prospective cohort

*Correspondence to: Dr M. Barba, Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, Temple University, Bio-Life Sciences Building,

studies on diabetes and cancer have shown a 1.3-fold increased risk for colorectal cancer and a 1.2-fold increased risk for postmenopausal breast cancer in diabetic patients [10, 11]. In major prospective cohort studies on glucose level and cancer risk, increased glucose levels were consistently associated with an increased risk of colorectal cancer [12]. Results for breast cancer were somewhat more inconsistent. Elevated baseline glucose levels appeared to be associated with an increased risk of both pre- and postmenopausal breast cancer in Korean women, but the association of interest was exclusively confirmed in postmenopausal women in the Austrian study and in premenopausal women in the Swedish study [13–15].

Experimental data substantiate the hypothesis that increases in blood glucose and factors related to its metabolism could affect carcinogenesis through effects on cellular energy metabolism. Abnormalities in glucose metabolism can turn into enhanced sensitivity to oxidative stress and mitochondrial dysfunction [16–19]. The resulting imbalance between the production of highly reactive molecular species, chiefly oxygen and nitrogen, and antioxidant defenses may significantly affect cancer risk, particularly in neoplasms with a strong metabolic component such as breast and colorectal cancers [20].

The aim of the present study was to investigate whether, in patients diagnosed with breast or colorectal cancers, circulating levels of pretreatment fasting glucose were predictive of resistance to targeted agents. Our working hypothesis was that an association between lower levels of the investigated biomarker and longer time to disease progression might exist in these patients.

patients and methods

study participants and setting

This study was a multidisciplinary investigation coordinated by the Italian National Cancer Institute Regina Elena in Rome together with La Sapienza University in Rome. The Division of Medical Oncology B at Regina Elena and the Department of Senology at G. Pascale provided data for breast cancer patients. The Department of Medical Oncology and Endocrinology at Federico II Medical School in Naples and the Department of Colorectal Medical Oncology at G. Pascale contributed data for colorectal cancer patients.

We included participants aged ≥18, diagnosed with histologically confirmed breast or colorectal cancer and who were treated with targeted agents from 1998 to 2009. Breast cancer patients were considered suitable for inclusion if they had received trastuzumab according to the indications released by the US FDA [http://www.cancer.gov/cancertopics/druginfo/fda-trastuzumab, (3 November 2011, date last accessed)]. We posed no restrictions regarding trastuzumab use in early, locally advanced or metastatic breast cancer, neither did we in reference to the administration schedule. We included women who received trastuzumab as a single agent or in combined regimens, at any dosage and duration. Women who received trastuzumab repeatedly, either according to the same or different schedules, were considered exclusively in reference to the first use of this drug.

We further included colorectal cancer patients who had received bevacizumab and/or cetuximab according to the indications and recommendations established by the US FDA [http://www.cancer.gov/cancertopics/druginfo/fda-bevacizumab, http://www.cancer.gov/cancertopics/druginfo/fda-cetuximab, (3 November 2011, date last accessed)]. Again, we posed no restrictions regarding the administration schedule. Patients who first received bevacizumab and were subsequently treated with cetuximab (or vice versa) were included in our database in reference to the agent that was first administered. If repeatedly treated with either bevacizumab or cetuximab, patients were considered exclusively in reference to the first administration. We excluded patients with previous or concomitant history of malignancy other than breast or colorectal cancer, as well as patients diagnosed with either type I or type II diabetes based on laboratory data and those whose pretreatment fasting glucose was ≥126 mg/dl [21].

data retrieving

Medical record retrieving was based on the close collaboration between a specifically trained medical assistant and the medical oncologists in charge of patient management and follow-up at the participating institutions. We reviewed the cases of breast and colorectal cancer patients diagnosed and treated between January 1998 and March 2009. For each patient, we sought to include data on demographics and anthropometrics, particularly body weight and height at baseline and at the end of follow-up. We further retrieved data on cancer features at the time of diagnosis (e.g. stage of disease), ascertainment of HER2/neu receptor status in breast cancer and EGFR and KRAS status in metastatic colorectal cancer patients, administered therapy and follow-up.

laboratory assays

Pretreatment fasting glucose was measured on venous blood collected at the time of (histologically confirmed) breast or colorectal cancer diagnosis and previous to any form of cancer therapy. Blood samples were collected in standardized conditions claiming overnight fasting and time at blood drawing between 7 and 10 am.

Glucose concentrations were locally determined using a Cobas analyzer with Roche hexokinase reagent. Central laboratories at the participating institutions were certified to an international management systems standard called ISO 9001 (ISO 9001:2000/2008).

immunohistochemistry, silver *in situ* hybridization and FISH

HER2 positivity was determined locally and defined as immunohistochemical staining of 3+ or 2+ with evidence of gene amplification at FISH. HER2 immunostaining was carried out using the polyclonal antibody A0485 (Dako, Milan, Italy). HER2 immunohistochemistry (IHC) positivity was determined according to the American Society of Clinical Oncology-College of American Pathologists (ASCO--CAP) guidelines [22].

Silver *in situ* hybridization (SISH) was used to assess *HER2* gene and Chr17 status (Inform HER2 DNA Probe, Inform Chr17 probe; Ventana, Roche Diagnostic, Milan, Italy). The HER2 and centromere on chromosome 17 dinitrophenol-labeled probes were visualized using the rabbit anti-dinitrophenol primary antibody and the ultraVIEW SISH Detection Kit. Case definition was carried out according to the ASCO–CAP guidelines [22].

IHC, DNA extraction and *KRAS* mutation analysis

Immunohistochemical stains for EGFR were locally carried out on 5-μ paraffin-embedded tissue sections using DAKO EGFR PharmDX kit (Dako). EGFR expression was defined positive as any membrane staining above background level was visualized. Results were further interpreted according to a quantitative score.

DNA for *KRAS* mutation analysis was extracted using the DNA extraction kit QIAmp DNA kit (Qiagen-Explera, Jesi, Italy). The DNA was used in a PCR to amplify the region of exon 2 of *KRAS*-containing codons

12 and 13. The PCR products were purified using Nucleospin Extract II Purification kit (M-Medical, Milan, Italy), sequenced using BigDye Terminator v 3.1 kit (Applied Biosystems, Monza, Italy) and analyzed with an ABI 3130 capillary electrophoresis system (Applied Biosystems). The presence of a heterozygous *KRAS* mutation was defined as the appearance of a mutant peak with a height of at least one-third of that of the wild type. In all the colorectal cancer patients, DNA was extracted from the primary tumor.

Extensive details on the procedures described above will be provided upon request.

statistical analyses

We examined distributions and computed descriptive statistics for all the variables of interest. We described the study participants' features (overall and by cancer site) and reported them through tertiles of pretreatment fasting glucose. We used means and standard deviations for continuous data as well as frequencies and percentage values for categorical data. Existing differences between mean values were evaluated using the Student's *T* or one-way analysis of variance test dependently on the number (two or more) of groups compared. We used the Pearson's Chi-square test of independence (two tailed) to assess the relationships between categorical variables.

We carried out survival analyses using the Kaplan–Meier product-limit method and applied the log-rank test to compare the survival curves through tertiles of fasting glycemia. Time to the development of resistance to targeted agents was calculated as the interval between the date at first trastuzumab/bevacizumab/cetuximab administration and (the date at) disease progression, last follow-up or death by cancer, whichever came first. We conducted survival analyses on the overall sample and on subsets obtained stratifying by cancer site, gender and, in women, menopausal status. Given the recognized role of KRAS status in predicting patients' important outcomes in metastatic colorectal cancer treated with cetuximab [23], we conducted a set of separate analyses excluding the 46 patients with unknown KRAS status.

The Cox proportional hazards model was used to further test the predictive role of fasting glucose on patients' important outcomes in multivariate analyses. Gender, age and body mass index (BMI) at cancer diagnosis were included as covariates. The model was further stratified by primary site of cancer (i.e. breast versus colorectal cancer). We also used stage at cancer diagnosis as a proxy variable for cancer burden and tested it for interaction in a separate Cox model.

Data on age at cancer diagnosis were not available for 10 patients, while BMI was unknown for 38 patients. Missing values for these two variables were replaced by their means calculated by cancer site and tertiles of fasting glucose, respectively.

We considered *P* values <0.05 statistically significant. All statistical analyses were carried out with the SPSS statistical software version 18 (SPSS Inc., Chicago, IL).

results

Overall, four hundred and twenty cancer patients were included in our analyses. Two hundred and eighteen patients had received a breast cancer diagnosis, while two hundred and two patients had been diagnosed with colorectal cancer. Mean age at cancer diagnosis was 53.4 ± 12.8. Females were more represented than men (298 versus 122), as well as postmenopausal women among females (160 of 298). Participants were more commonly married (221 of 420) than separated, single or widowed. Data related to smoking status were only partly available, with current/past smokers representing 13.6% of our sample. Means and standard deviations for height (cm), weight (kg) and BMI (m^2/kg) at baseline were 162.6 ± 7.9, 66.2 ± 13.1 and 25.5 ± 4.3, respectively. The median duration of follow-up was 20 months (1–128; data available upon request).

In Table 1, our study participants were compared by primitive cancer site. Cancer patients significantly differed by age at cancer diagnosis, menopausal status, marital status, anthropometrics at baseline and stage at cancer diagnosis. Breast cancer patients were more likely to be younger, premenopausal and with a lower disease stage at cancer diagnosis when compared with colorectal cancer patients (49.4 ± 12.2 versus 57.8 ± 12.1, $P < 0.001$; 74.5% versus 25.5%, $P = 0.025$ and 98.8% versus 1.2%, $P < 0.001$, respectively). Separated, single and widowed participants were significantly more common among breast cancer patients than in the colorectal cancer group (92.9%, 76.5% and 66.7% versus 7.1%, 23.5% and 33.3%, $P = 0.019$, respectively). Furthermore, women diagnosed with breast cancer showed lower height and body weight at baseline (161.2 ± 6.5 versus 165 ± 9.2, $P = 0.008$, respectively).

Cancer patient characteristics through tertiles of pretreatment fasting glucose appear in Table 2. Patients in the first tertile were more likely to be younger, single, female and, if so, premenopausal when compared with participants in the third tertile (48.9 ± 13.6 versus 57.5 ± 11.4, $P < 0.001$; 60%

Table 1. Study participant characteristics by primitive cancer site

	Primitive cancer site		*P* value[a]
	Colorectal	Breast	
Age at cancer diagnosis (years), mean ± SD	57.8 ± 12.1	49.4 ± 12.2	<0.001
Gender, *n* (%)			
Male	122 (100.0)	0 (0)	<0.001
Female	96 (32.2)	202 (67.8)	
Menopausal status, *n* (%)			
Premenopausal	35 (25.5)	102 (74.5)	0.025
Postmenopausal	61 (38.1)	99 (61.9)	
Marital status, *n* (%)			
Married	88 (39.8)	133 (60.2)	0.019
Separated	1 (7.1)	13 (92.9)	
Single	12 (23.5)	39 (76.5)	
Widowed	7 (33.3)	14 (66.7)	
Smoking status, *n* (%)			
Yes	14 (24.6)	43 (75.4)	0.451
No	34 (19.2)	143 (80.8)	
Height at baseline (cm), mean ± SD	165 ± 9.2	161.2 ± 6.5	0.001
Weight at baseline (kg), mean ± SD	69.1 ± 12.8	64.8 ± 13.1	0.008
BMI at baseline (m^2/kg), mean ± SD	25.7 ± 3.8	25.2 ± 4.8	0.341
Stage at cancer diagnosis, *n* (%) (TNM)			
I	1 (1.2)	85 (98.8)	<0.001
II	4 (100.0)	0 (0)	
III	11 (91.7)	1 (8.3)	
IV	87 (51.5)	82 (48.5)	

[a]Comparisons were carried out with the Pearson's Chi-square test for the categorical variables and Student's *T* test for continuous variables.
SD, standard deviation; BMI, body mass index; TNM, tumor–node–metastasis.

Table 2. Study participant characteristics by tertiles of pretreatment fasting glucose

	Tertiles of glycemia at baseline (mg/dl)			*P* value[a]
	≤88	89–98	≥99	
Age at cancer diagnosis (years), mean ± SD	48.9 ± 13.6	54.4 ± 11.6	57.5 ± 11.4	<0.001
Gender, *n* (%)				
Male	24 (20.3)	44 (37.3)	50 (42.4)	0.001
Female	116 (39.3)	97 (32.9)	82 (27.8)	
Menopausal status, *n* (%)				
Premenopausal	70 (51.9)	40 (29.6)	25 (18.5)	<0.001
Postmenopausal	46 (28.9)	57 (35.9)	56 (35.2)	
Marital status, *n* (%)				
Married	78 (35.6)	76 (34.7)	65 (29.7)	<0.001
Separated	5 (35.7)	3 (21.4)	6 (42.9)	
Single	30 (60.0)	12 (24.0)	8 (16.0)	
Widowed	4 (19.0)	3 (14.3)	14 (66.7)	
Smoking status, *n* (%)				
Yes	28 (49.1)	16 (28.1)	13 (22.8)	<0.001
No	72 (40.7)	59 (33.3)	46 (26.0)	
Height at baseline (cm), mean ± SD	162.5 ± 8.1	162.4 ± 7.6	162.8 ± 8.0	0.952
Weight at baseline (kg), mean ± SD	63.3 ± 12.9	66.2 ± 13.2	70.2 ± 12.4	0.001
BMI at baseline (m^2/kg), mean ± SD	24.8 ± 4.4	25.4 ± 4.3	26.3 ± 4.1	0.029
Stage at cancer diagnosis, *n* (%) (TNM)				
I	36 (41.9)	29 (33.7)	21 (24.4)	0.508
II	1 (25)	1 (25)	2 (50)	
III	3 (27.3)	2 (18.2)	6 (54.5)	
IV	66 (40.0)	51 (30.9)	48 (29.1)	

[a]Comparisons were carried out with the Pearson's Chi-square test for categorical variables and one-way ANOVA for continuous variables.
SD, standard deviation; BMI, body mass index; TNM, tumor–node–metastasis; ANOVA, analysis of variance.

versus 16%, $P < 0.001$; 39.3% versus 27.8%, $P = 0.001$ and 51.9% versus 18.5%, $P < 0.001$; respectively). Cancer patients in the first tertile of pretreatment fasting glucose were also more commonly smokers and showed lower body weight and BMI at baseline (49.1% versus 22.8%, $P < 0.001$; 63.3 ± 12.9 versus 70.2 ± 12.4, $P = 0.001$ and 24.8 ± 4.4 versus 26.3 ± 4.1, $P = 0.029$, respectively). Figure 1 shows the time to disease progression through tertiles of pretreatment fasting glucose for the overall sample. At 60 months, 65% of cancer patients in the lowest tertile (≤88 mg/dl) did not experience disease progression compared with 34% in the second and third tertiles ($P = 0.001$). When stratifying by gender (Figure 2), 76% of female participants in the lowest tertile showed no progression compared with 49% in the remaining tertiles ($P = 0.015$). We further stratified analyses by menopausal status and primitive cancer site. In supplemental Figure S1 (available at *Annals of Oncology* online), premenopausal women in the lowest tertile showed a longer, although of only borderline significance, time to disease progression compared with women in the highest tertile (74% versus 39%, $P = 0.053$). In supplemental Figure S2 (available at *Annals of Oncology* online), there was an indication for longer time to disease progression in breast cancer participants with lower pretreatment glucose levels compared with breast cancer patients in the highest tertile (87% versus 54%, $P = 0.053$). The exclusion of the 46 colorectal cancer patients with unknown KRAS status did not affect our estimates (data available upon request).

Cox proportional hazards models of variables associated with time to disease progression in breast and colorectal cancer patients overall and by site of primitive cancer are presented in supplemental Tables S1 and S2 (available at *Annals of Oncology* online). As shown in Table S1 (available at *Annals of Oncology* online), in multivariate analysis including gender, age at cancer diagnosis and BMI as covariates, the predictive role of pretreatment fasting glucose on time to disease progression was confirmed. Cancer patients in the second and third tertiles showed a significantly shorter time to disease progression compared with those in the first tertile [hazard ratio (HR) 1.86, 95% confidence interval (CI) 1.10–3.16 and HR 1.76, 95% CI 1.01–3.08, respectively]. However, when stratified by primary site of cancer (Table S2, available at *Annals of Oncology* online), the Cox model confirmed these results only in breast cancer patients in the first tertile compared with the third (HR 4.07, 95% CI 1.29–12.85). The Cox model testing the interaction between stage at cancer diagnosis and pretreatment fasting glucose produced no significant results ($P = 0.640$).

discussion

According to the results of our historic cohort study, in breast and metastatic colorectal cancer patients treated with targeted agents, lower levels of pretreatment fasting glucose were predictive of longer time to disease progression. When stratifying by gender, pretreatment fasting glucose was a stronger predictor in women than in men. There was also a

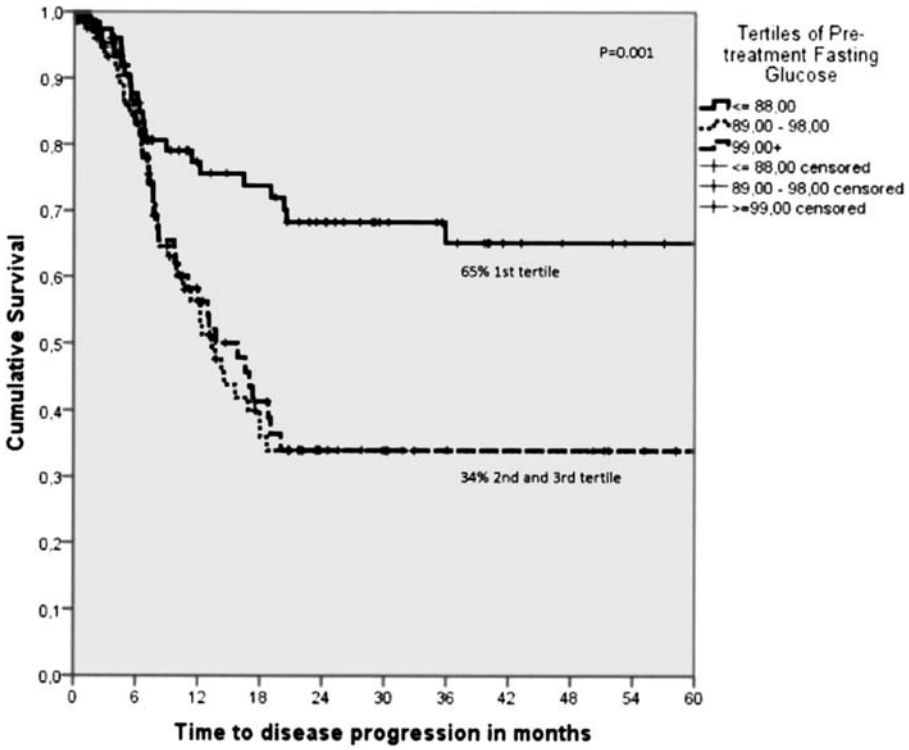

Figure 1. Time to disease progression in months.

suggestion for a role of menopausal status and primitive cancer site in modifying the association of interest, with results of borderline significance in premenopausal women and in patients diagnosed with breast cancer. Our results do not support the existence of a dose–response relationship between the biomarker of interest and treatment outcome. Indeed, breast and colorectal cancer patients in the second and third tertiles showed no difference in terms of time to disease progression. Though on highly speculative ground, this seems to suggest that increases in pretreatment fasting glucose might affect treatment outcomes across a relatively restricted range of normal values. In our historical cohort, the latter range seems to fall within the first tertile (i.e. ≤88 mg/dl). Conversely, further increases do not necessarily translate into substantial worsening of the outcomes considered. Our figures seemed to suggest a relevant role of primary site of cancer on the association of interest, which was confirmed in multivariate analyses stratified accordingly. The Cox model showed a significant longer time to disease progression exclusively in breast cancer patients in the first tertile compared with the third ($P = 0.017$). Conversely, fasting glucose had no predictive role on time to disease progression in colorectal cancer patients. Differences in tumor burden between these two subpopulations might help explain this result. Though we lack adequate data to precisely estimate the tumor burden, based upon the stage at cancer diagnosis and indications to trastuzumab administration, we might speculate that our breast cancer patients were quite equally distributed among the early and advanced stages. Conversely, most of the colorectal cancer patients were metastatic at diagnosis and all of them were metastatic at target therapy administration. In these patients, the investigated association might have been obscured by the greater cancer burden and the consequent more rapid onset of drug resistance. However, when testing the interaction between stage at diagnosis and pretreatment fasting glucose, no significant results were obtained.

The retrospective nature of our study design represents the main source of our study limitations. The retrospective design has limited us in availability of data potentially relevant to the investigated association, e.g. smoking status, number and site of metastatic involvement. This is extremely common when relying on data primarily collected for clinical purposes in a clinical setting. Furthermore, among the potential predictors of resistance to targeted agents related to glucose metabolism, we exclusively investigated fasting glucose while not considering other potentially relevant markers, such as baseline insulin, insulin-like growth factor-I (IGF-I) and insulin-like growth factor proteins. Unfortunately, no biological samples and related consent forms were available for the included participants. Finally, we based our analyses on a single pretreatment fasting glucose determination. We are conscious that glucose levels from a single serum sample may not adequately characterize the exposure of interest. On the other hand, although available, the results of further glucose determinations may have been influenced by administered treatments.

Our study also has several important strengths. First, for each of our patients, the standard assay of pretreatment fasting glucose was run by the central laboratory of the pertinent participating cancer institute. This is a major strength of our study. Indeed, institutional central laboratories have active and ongoing quality control protocols, which ensure high-quality biomarker data. Secondly, given that data were collected via retrieval of medical records, this study provided a relatively

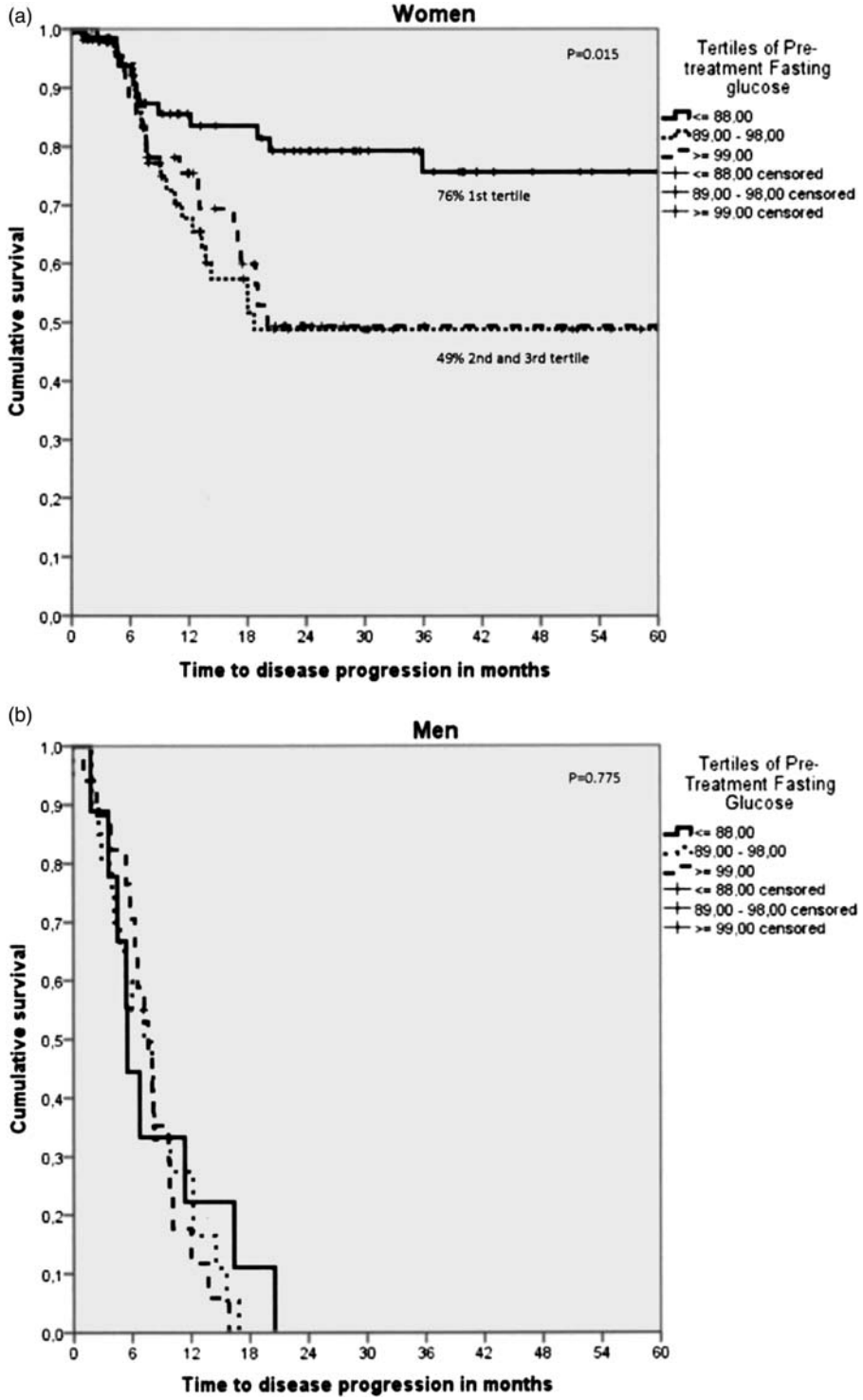

Figure 2. Time to disease progression in months. Analyses stratified by gender.

inexpensive and fast way to investigate the stated hypothesis. Abstraction from the medical records was carried out by a specifically trained medical assistant in close collaboration with the medical oncologists who had prospectively followed the patients included in our analyses. This increases our confidence in the quality of the information gathered. Furthermore, the pretreatment assessment of the exposure of interest (fasting glucose) should preserve the temporality of the observed associations, an important criterion to assess causality. Finally, we explored a completely novel and potentially highly informative relationship.

Our study results are barely comparable with the currently available epidemiologic evidence. It is worthy to note that all previous research in the pertinent area, that is the impact of glucose-related metabolism on breast and colorectal carcinogenesis, has focused either on breast and/or colorectal

cancer incidence and/or mortality. Among the prospective studies conducted so far, only a few found no associations [24, 25], while the majority showed significantly increased risk of cancer development or death with increased glucose [10–15, 24, 26–37].

From a biological perspective, the interplay between factors related to glucose metabolism and the molecular targets of the therapeutic agents of interest might help interpret our study results. Indeed, data from the preclinical setting have shown that insulin promotes the transcription of several genes, including those encoding the glucose transporter GLUT1 and VEGF [3]. IGF-I increases the expression of VEGF messenger RNA and the production of VEGF protein by COLO 205 colon carcinoma cells [4] and enhances the expression of VEGF in osteoblasts [5]. In addition, evidence of the tight interplay between insulin-like growth factor-I receptor (IGF-IR) and EGFR emerges from a number of studies. IGF-1R activation is crucial for the mitogenic and transforming activity of the EGFR [6, 7].

In conclusion, the present study provides novel evidence on the predictive role of pretreatment fasting glucose levels in the development of resistance to cancer treatment. These findings may have important clinical implications in the management and prognosis for cancer patients. In fact, if additional prospective and experimental studies corroborate our findings, two main consequences could be hypothesized. First, these patients would be subject to very tight blood sugar control. Secondly, the threshold for treatment of blood glucose would change dramatically. This could potentially affect time to disease progression and increase survival, leading the way to new avenues for exploring underlying resistance to targeted agent-based regimens.

acknowledgements

We thank Tania Merlino for editorial assistance. Merlino did not receive compensation for her assistance apart from her employment at the institution where the study was conducted.

funding

Regina Elena National Cancer Institute (06/08RC03).

disclosure

The authors declare no conflict of interest.

references

1. Jones KL, Buzdar AU. Evolving novel anti-HER2 strategies. Lancet Oncol 2009; 10 (12): 1179–1187.
2. Capdevilla J, Saura C, Macarulla T et al. Monoclonal antibodies in the treatment of advanced colorectal cancer. Eur J Surg Oncol 2007; 33 (Suppl 2): S23–S24.
3. Zelzer E, Levy Y, Kahana C et al. Insulin induces transcription of target genes through the hypoxia-inducible factor HIF-1alpha/ARNT. EMBO J 1998; 17: 5085–5094.
4. Warren R, Yuan H, Matli MR et al. Induction of vascular endothelial growth factor by insulin-like growth factor 1 in colorectal carcinoma. J Biol Chem 1996; 271: 29483–29488.
5. Goad D, Rubin J, Wang H et al. Enhanced expression of vascular endothelial growth factor in human SaOS-2 osteoblast-like cells and murine osteoblasts induced by insulin-like growth factor I. Endocrinology 1996; 137: 2262–2268.
6. Coppola D, Ferber A, Miura M et al. A functional insulin-like growth factor I receptor is required for the mitogenic and transforming activities of the epidermal growth factor receptor. Mol Cell Biol 1994; 14: 4588–4595.
7. Roudabush FL, Pierce KL, Maudsley S et al. Transactivation of the EGF receptor mediates IGF-1-stimulated shc phosphorylation and ERK1/2 activation in COS-7 cells. J Biol Chem 2000; 275: 22583–22589.
8. Wang D, Li W, Jiang W et al. Autocrine TGFalpha expression in the regulation of initiation of human colon carcinoma growth. J Cell Physiol 1998; 177: 387–395.
9. Wang D, Patil S, Li W et al. Activation of the TGFalpha autocrine loop is downstream of IGF-I receptor activation during mitogenesis in growth factor dependent human colon carcinoma cells. Oncogene 2002; 21: 2785–2796.
10. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007; 121: 856–862.
11. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 2005; 97: 1679–1687.
12. Pisani P. Hyper-insulinaemia and cancer, meta-analyses of epidemiological studies. Arch Physiol Biochem 2008; 114: 63–70.
13. Jee SH, Ohrr H, Sull JW et al. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005; 293(2): 194–202.
14. Rapp K, Schroeder J, Klenk J et al. Fasting blood glucose and cancer risk in a cohort of more than 140000 adults in Austria. Diabetologia 2006; 49(5): 945–952.
15. Stattin P, Björ O, Ferrari P et al. Prospective study of hyperglycemia and cancer risk. Diabetes Care 2007; 30(3): 561–567.
16. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004; 4: 579–591.
17. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. Proc Nutr Soc 2001; 60: 91–106.
18. Quagliaro L, Piconi L, Assaloni R et al. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. Diabetes 2003; 52(11): 2795–2804.
19. Rolo AP, Palmeira CM. Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress. Toxicol Appl Pharmacol 2006; 212(2): 167–178.
20. Hopkins MH, Ferdirko V, Jones DP et al. Antioxidant micronutrients and biomarkers of oxidative stress and inflammation in colorectal adenoma patients: results from a randomized, controlled clinical trial. Cancer Epidemiol Biomarkers Prev 2010; 19(3): 850–858.
21. American Diabetes Association. Clinical practice recommendations. Diabetes Care 2008; 31Suppl 1S1–S108.
22. Wolff AC, Hammond ME, Schwartz JN et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med 2007; 131(1): 18–43.
23. Markman B, Javier Ramos F, Capdevila J, Tabernero J. EGFR and KRAS in colorectal cancer. Adv Clin Chem2010; 51: 71–119.
24. Tsushima M, Nomura A, Lee J, Stemmermann GN. Prospective study of the association of serum triglyceride and glucose with colorectal cancer. Dig Dis Sci 2005; 50: 499–505.
25. Wei EK, Ma J, Pollak MN et al. C-peptide, insulin-like growth factor binding protein-1, glycosylated hemoglobin, and the risk of distal colorectal adenoma in women. Cancer Epidemiol Biomarkers Prev 2006; 15(4): 750–755.
26. Grote VA, Becker S, Kaaks R. Diabetes mellitus type 2—an independent risk factor for cancer?. Exp Clin Endocrinol Diabetes 2010; 118(1): 4–8.
27. Muti P, Quattrin T, Grant BJ et al. Fasting glucose is a risk factor for breast cancer: a prospective study. Cancer Epidemiol Biomarkers Prev 2002; 11(11): 1361–1368.
28. Wei EK, Ma J, Pollak MN et al. A prospective study of C-peptide, insulin-like growth factor-I, insulin-like growth factor binding protein-1, and the risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 2005; 14: 850–855.
29. Ahmed RL, Schmitz KH, Anderson KE et al. The metabolic syndrome and risk of incident colorectal cancer. Cancer 2006; 107(1): 28–36.

30. Colangelo LA, Gapsture SM, Gann PH et al. Colorectal cancer mortality and factors related to the insulin resistance syndrome. Cancer Epidemiol Biomarkers Prev 2002; 11(4): 385–391.
31. Flood A, Mai V, Pfeiffer R et al. Elevated serum concentrations of insulin and glucose increase risk of recurrent colorectal adenomas. Gastroenterology 2007; 133(5): 1423–1429.
32. Schoen RE, Tangen CM, Kuller LH et al. Increased blood glucose and insulin, body size, and incident colorectal cancer. J Natl Cancer Inst 1999; 91(13): 1147–1154.
33. Limburg PJ, Stolzenberg-Solomon RZ, Vierkant RA et al. Insulin, glucose, insulin resistance, and incident colorectal cancer in male smokers. Clin Gastroenterol Hepatol 2006; 4(12): 1514–1521.
34. Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. Br J Cancer 2001; 84(3): 417–422.
35. Platz EA, Hankinson SE, Rifai N et al. Glycosylated hemoglobin and risk of colorectal cancer and adenoma (United States). Cancer Causes Control 1999; 10 (5): 379–386.
36. Saydah SH, Platz EA, Rifai N et al. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2003; 12(5): 412–418.
37. Trevisan M, Liu J, Muti P et al. Markers of insulin resistance and colorectal cancer mortality. Cancer Epidemiol Biomarkers Prev 2001; 10(9): 937–941.

Annals of Oncology 23: 1845–1853, 2012
doi:10.1093/annonc/mdr539
Published online 21 November 2011

Evaluation of glomerular filtration rate estimation by Cockcroft–Gault, Jelliffe, Wright and Modification of Diet in Renal Disease (MDRD) formulae in oncology patients

N. L. Ainsworth[1]*, A. Marshall[2], H. Hatcher[1], L. Whitehead[1], G. A. Whitfield[1] & H. M. Earl[1,3,4]

[1]Oncology Centre, Addenbrooke's Hospital, Cambridge; [2]Warwick Clinical Trials Unit, University of Warwick, Coventry; [3]Department of Oncology, University of Cambridge, Cambridge; [4]National Institute for Health Research, Cambridge Biomedical Research Centre, Cambridge, UK

Received 15 February 2011; revised 29 August 2011; accepted 10 October 2011

Background: The aim was to evaluate the accuracy of Cockcroft–Gault, Jelliffe, Wright and Modification of Diet in Renal Disease (MDRD) formulae as a substitute for the gold standard measure of glomerular filtration rate (GFR) using chromium 51 EDTA.
Patients and methods: Retrospective analysis of GFR measurements in oncology patients from a University Teaching Hospital over 3 years was carried out. Bias and precision of estimates of GFR were compared with measured GFR.
Results: Six hundred and sixty patients with measured GFR (median 90 ml/min, range 23–179 ml/min) were identified. Cockcroft–Gault produced the smallest bias (median percentage error −1.4%) and highest precision (median absolute percentage error 14.0%) and was the most accurate for carboplatin dosing. For patients >30% over their ideal body weight (IBW), using IBW + 30% in the Cockcroft–Gault formula was more precise than using actual body weight or IBW. The Wright formula was most accurate for patients aged 70 + years and patients with a body mass index (BMI) ≥30 but overestimated GFR when GFR < 50 ml/min.
Conclusions: When measured GFR is unavailable, we advise estimating GFR using the Cockcroft–Gault formula and using IBW + 30% for patients weighing >30% over their IBW. If the GFR is ≥50 ml/min and the patient is >70 years and/or BMI ≥30, the Wright formula gives the best estimate of GFR.
Key words: carboplatin, Cockcroft–Gault, estimation, formula, glomerular filtration rate

introduction

Many patients having therapy for cancer require assessment of renal function for dosing of cytotoxic chemotherapy agents. Carboplatin in particular is calculated using a targeted area under the plasma carboplatin concentration time curve (AUC) instead of using body surface area (BSA) [1]. The Calvert equation is used for dosing carboplatin and incorporates the glomerular filtration rate (GFR) as its key variable (Figure 1). It is therefore essential to establish an accurate GFR. Early trials used 24-h urine creatinine collection and inulin excretion;

*Correspondence to: Dr N. L. Ainsworth, Oncology Centre, Addenbrooke's Hospital, Box 193, Hills Road, Cambridge CB2 0QQ, UK. Tel: + 44-0-1223-336800; Fax: + 44-0-1223763120; E-mail: nicola.ainsworth@cancer.org.uk